Journal of Cardiology 66 (2015) 232–238

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

Effects of human atrial natriuretic peptide on myocardial performance and energetics in heart failure due to previous myocardial infarction

Toru Ozawa (MD)[a], Toshiro Shinke (MD, PhD, FJCC)[b,*], Junya Shite (MD, PhD, FJCC)[b], Hideyuki Takaoka (MD, PhD)[b], Nobutaka Inoue (MD, PhD)[a], Hidenari Matsumoto (MD, PhD)[b], Satoshi Watanabe (MD, PhD)[b], Ryohei Yoshikawa (MD)[b], Hiromasa Otake (MD, PhD)[b], Daisuke Matsumoto (MD, PhD)[b], Daisuke Ogasawara (MD)[b], Mitsuhiro Yokoyama (MD, PhD, FJCC)[b], Ken-ichi Hirata (MD, PhD)[b]

[a] *Kobe Rosai Hospital, Department of Cardiology, Kobe, Japan*
[b] *Kobe University Graduate School of Medicine, Division of Cardiovascular Medicine, Department of Internal Medicine, Kobe, Japan*

ARTICLE INFO

Article history:
Received 10 June 2014
Received in revised form 6 December 2014
Accepted 28 December 2014
Available online 23 February 2015

Keywords:
Cardiac mechano-energetics
Conductance catheter
Cyclic guanosine monophosphate
E_{es}

ABSTRACT

Background: Human atrial natriuretic peptide (hANP) and spontaneous nitric oxide (NO) donor share cyclic guanosine monophosphate (cGMP) as a second messenger, but their effect on myocardium may differ. We compared the effect of hANP and sodium nitroprusside (SNP) on left ventricular (LV) mechano-energetics in heart failure (HF).

Methods: Ten patients with HF due to previous myocardial infarction (LV ejection fraction: 45 ± 3%) were instrumented with conductance and coronary sinus thermodilution catheters. LV contractility (E_{es}: slope of end-systolic pressure–volume relation) and the ratio of LV stroke work (SW) to myocardial oxygen consumption (SW/MVO_2 = mechanical efficiency) were measured in response to intravenous infusion of ANP (0.05 μg/kg/min) or SNP (0.3 μg/kg/min) to lower blood pressure by at least 10 mmHg, and changes in plasma cGMP.

Results: SNP had no effect on E_{es}, SW, or MVO_2, thus SW/MVO_2 remained unchanged (40.54 ± 5.84% to 36.59 ± 5.72%, $p = 0.25$). ANP increased E_{es}, and decreased MVO_2 with preserved SW, resulting in improved SW/MVO_2 (40.49 ± 6.35% to 50.30 ± 7.96%, $p = 0.0073$). Infusion of ANP (10.42–34.95 pmol/ml, $p = 0.0003$) increased cGMP levels, whereas infusion of SNP had no effect (10.42–12.23 pmol/ml, $p = 0.75$).

Conclusions: Compared to SNP, the ANP-dependent increase in cGMP may ameliorate myocardial inotropy and energetics in HF.

Introduction

Congestive heart failure (CHF) is a complex syndrome that results from various underlying conditions, including acute and chronic ischemic heart disease, cardiomyopathies, myocarditis, and pressure overload, that lead to an inability to pump blood at an output sufficient to meet the requirements of tissues in the body. Current therapies for CHF include loop diuretics to reduce intravascular volume, vasodilators to reduce vascular resistance, and inotropic agents to increase myocardial contractility.

Vasodilatation using a nitric oxide (NO) donor such as nitroglycerin and sodium nitroprusside (SNP) is a widely used therapeutic strategy for CHF. NO has vasodilatation effects in vascular smooth muscle cells via the activation of soluble guanylate cyclase and an increase in intracellular levels of guanosine 3′,5′-cyclic monophosphate (cGMP), an intracellular messenger. In addition to vasodilatation, several experimental studies have suggested that NO donors affect cardiac contractility. De Mulder et al. demonstrated that SNP enhances the left ventricular (LV) contractile response to β-adrenergic stimulation [1]. In contrast, Shinke et al. demonstrated that inhibition of endogenous NO synthase enhances the LV contractile response to β-adrenergic stimulation [2]. The precise effects of NO on cardiac function and mechano-energetics in patients with CHF, however, have not been investigated clinically.

* Corresponding author at: Kobe University Graduate School of Medicine, Division of Cardiovascular Medicine, Department of Internal Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan. Tel.: +81 78 382 5846; fax: +81 78 382 5859.
E-mail address: shinke@med.kobe-u.ac.jp (T. Shinke).

http://dx.doi.org/10.1016/j.jjcc.2014.12.020
0914-5087/

Atrial natriuretic peptide (ANP) induces various biologic responses via binding the particulate guanylate cyclase-coupled receptor, that is, the natriuretic peptide receptor-A (NPR-A) [3], and this natriuretic peptide utilizes cGMP as a second messenger similarly to NO. In addition to its potent natriuretic and vasodilatory properties, ANP has various other beneficial effects, such as anti-inflammatory effects, suppression of sympathetic tone and catecholamine production, and inhibition of the renin–angiotensin system [4–6].

The effect of ANP on myocardial contractility, however, is controversial. Ohte et al. reported that ANP had a negative inotropic effect in both normal dogs and dogs with CHF [7]. On the other hand, Lainchbury et al. demonstrated that ANP had a positive inotropic effect in normal dogs, and no inotropic effect in dogs with CHF [8]. Mizuno et al. demonstrated that ANP administration increased E_{es}, an index of contractility, in patients with CHF [9].

Given these various potent biologic activities, clarification of the effects of ANP on contractility and cardiac mechano-energetics is important toward establishing a therapeutic strategy for CHF. In the present study, we examined the effects of an NO donor and ANP on cardiac performance and mechano-energetics in patients with LV dysfunction.

Methods

Patient population

Studies were performed in 10 patients (mean age 68.1 ± 9.5 years, men/women = 5/5) with prior myocardial infarction (MI). They underwent diagnostic cardiac catheterization for evaluation of heart function at least 1 month after the onset of MI.

All patients received percutaneous coronary stenting within 48 h of the onset of symptoms and had no residual epicardial coronary stenosis, dyskinetic LV wall motion, or more than moderate mitral valve regurgitation at the time of this study protocol. All patients were in sinus rhythm and were diagnosed with New York Heart Association functional class II CHF. Before cardiac catheterization, angiotensin-converting enzyme inhibitors and β-blockers were withheld for at least for 24 h and more than 72 h, respectively. Written informed consent was obtained from all patients, and the study protocol was approved by the Institutional Committee on Human Research at Kobe University Hospital.

Cardiac catheterization procedure

Patients had undergone routine right and left heart catheterization, left ventriculography, and coronary arteriography under fasting conditions without medication. A 6F conductance catheter (CardioDynamics, Rijnsberg, The Netherlands) was advanced into the LV through the right radial artery, and a 2F Millar Instruments catheter (Millar Instruments, Houston, TX, USA) was advanced into the LV through the lumen of the conductance catheter. An 8F coronary thermodilution catheter (Cordis Webster, Inc., Diamond Bar, CA, USA) was then advanced into the coronary sinus through the right jugular vein. The conductance catheter was attached to a stimulator/processor (Leycom Sigma-5, CardioDynamics). The electrocardiogram and hemodynamic parameters were recorded on a strip-chart recorder. Each measurement of the hemodynamic parameters was obtained as the mean value of 8–10 consecutive sinus beats.

Assessment of LV cardiac mechano-energetics

Coronary sinus blood flow (CSF) was measured with the previously described thermodilution technique [10]. Coronary blood was sampled from the distal lumen of the coronary thermodilution catheter for oximetry and determination of myocardial oxygen consumption (MVO_2). MVO_2 per minute was calculated as the product of CSF (ml/min) and the arterial-coronary sinus oxygen content difference (vol%) divided by heart rate to yield MVO_2 per beat (ml O_2/beat).

As previously described [11,12], pressure–volume loops for the sequence beats during the transient reduction in the preload by the Valsalva maneuver were recorded over 8–10 beats, and several pressure–volume loops were obtained from one subject. LV contractility is expressed as E_{es}, which is the slope of the linear end-systolic pressure–volume relation (ESPVR), as shown in Fig. 1 [13]. E_{es} is applied to the LV of the intact animal and humans as a load-independent index of myocardial contractility [14].

Effective arterial elastance (E_a) is a variable that incorporates the values of Windkessel model elements and heart rate as the ratio of end-systolic pressure to stroke volume, and corresponds to the slope of the line connecting the end-systolic pressure–volume point and the end-diastolic point on the volume axis [15]. The ratio of effective E_a to ventricular elastance (E_a/E_{es}) represents ventriculoarterial coupling. We normalized E_{es} and E_a (mmHg/ml/m^2) to the body surface area to permit comparison among patients in the present study, as described previously [13].

The rate of LV relaxation was analyzed using Tau. Tau is the time constant of LV pressure decay during isovolumic relaxation, quantified from a plot of $-dP/dt$ vs P ($P = P_0 e^{-t/T} + P_b$), where P is LV pressure, t is the time from peak $-dP/dt$, T is the time constant of isovolumic pressure decay, and P_0 and P_b are constants determined by the data [2,16].

Stroke work (SW) was calculated as the area bound by the pressure–volume trajectory of 1 beat. Systolic pressure–volume area (PVA) was calculated as the area bound by the ESPVR, end-diastolic pressure–volume relation (EDPVR), and the systolic pressure–volume trajectory of 1 beat. Mechanical efficiency was calculated as the ratio of SW (J/beat) to MVO_2 per beat (J/beat), where 1 mmHg/ml SW and 1 ml O_2 of oxygen consumption correspond to 1.33×10^{-4} and 20 J, respectively [17].

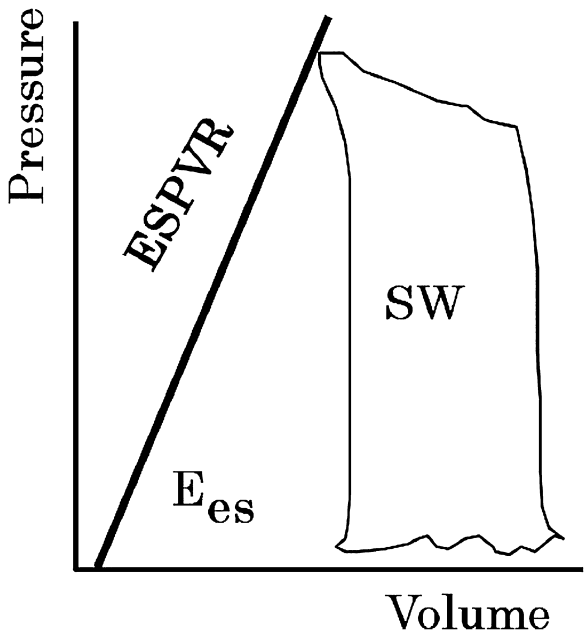

Fig. 1. LV pressure–volume relation. LV pressure–volume relation assessed by manometer-tipped LV conductance catheter. LV, left ventricular; E_{es}, slope of the LV end-systolic pressure–volume relation; SW, stroke work (J) calculated as the area bound by the pressure–volume trajectory of 1 beat; ESPVR, end-systolic pressure–volume relation.

Study protocol

Control study

After routine right and left heart catheterization, atrial pacing was started at 90 bpm or at 15 bpm above the baseline heart rate. Atrial pacing was continued for the duration of the study. At least 20 min after catheterization for stabilization of hemodynamics, the pressure–volume loops and CSF were measured, and blood gas samples were extracted from the coronary sinus and LV. Plasma cGMP levels were measured from the coronary sinus. ESPVR was obtained during the Valsalva maneuver.

Sodium nitroprusside and atrial natriuretic peptide study

After completion of the control study, SNP in 5% glucose was intravenously administered via the sheath lumen of the right jugular vein for 15 min. After steady hemodynamic and contractile states were achieved, the effects of SNP on cardiac mechano-energetics were evaluated as in the control study. Sufficient data were obtained, including the pressure volume curve, CSF, and ESPVR.

After evaluating the effects of SNP, the SNP infusion was discontinued and hemodynamic variables were monitored for at least 20 min until they returned to control values. After confirmation that the effect of SNP had vanished completely and hemodynamic variables returned to control steady states, the same measurements were repeated as a re-control study. The effects of ANP on cardiac mechano-energetics were then evaluated in the same way. In the ANP study, genetic recombinant α-human atrial natriuretic peptide (hANP) in 5% glucose was administered for 0.05 μg/kg/min via the same route as SNP infusion for 15 min. After stabilization of hemodynamic variables was confirmed, the same measurements were repeated.

On the basis of our preliminary study, the SNP and hANP doses were set at 0.3 μg/kg/min and 0.05 μg/kg/min, respectively, because we confirmed that the systemic blood pressure depressant effects by these two drugs were almost equivalent, and these concentrations were within clinically therapeutic doses. In 5 of the 10 patients enrolled in this study, the order of the administration of SNP and hANP was reversed to control for the effects of the administration order of the drug.

Statistical analysis

Data are shown as mean ± SEM. ESPVR values were obtained through linear regression analysis. The effects of SNP and ANP were analyzed independently with a paired *t* test with Bonferroni's correction for multiple comparisons. Drug-induced changes were analyzed with two-way repeated measures analysis of variance. A *p*-value less than 0.05 was considered significant.

Table 1
Baseline characteristics of the study population.

EF (%)	45.1 ± 3.1
MAP (mmHg)	93.6 ± 6.0
LVSP (mmHg)	131.8 ± 9.5
LVEDP (mmHg)	16.3 ± 2.5
RA (mmHg)	8.0 ± 0.6
PCWP (mmHg)	12.7 ± 2.2
CI (l/min/m^2)	2.7 ± 0.2
Peak +d*P*/d*t* (mmHg/s)	1904 ± 93
Tau (ms)	48.1 ± 2.6
Peak −d*P*/d*t* (mmHg/s)	2209 ± 398

EF, left ventricular ejection fraction; MAP, mean arterial pressure; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; RA, mean right atrial pressure; PCWP, mean pulmonary artery wedge pressure; CI, cardiac output/body index; Peak +d*P*/d*t*, peak positive d*P*/d*t*; Tau, time constant of LV pressure decay during isovolumic relaxation; Peak −d*P*/d*t*, peak negative d*P*/d*t*.

Results

Patient characteristics

Baseline characteristics of the study subjects are shown in Table 1. None of the study subjects developed significant narrowing of the main coronary arteries. None of the patients had significant mitral regurgitation or a trans-aortic valve pressure gradient. Ejection fractions, +d*P*/d*t*, −d*P*/d*t*, and Tau were 45.1 ± 3.1, 1904 ± 93, 2209 ± 298, and 48.1 ± 2.6, respectively. Thus, CHF in the subjects in the present study was associated with mild or moderate LV systolic dysfunction (EF ranging from 0.29 to 0.54).

Influence of SNP and ANP on hemodynamics

Effects of SNP and ANP on hemodynamic variables are summarized in Table 2. Both SNP and ANP decreased LV systolic pressure (−16 ± 3% and −9 ± 2%, respectively, $p = 0.06$) and LVEDP (−26 ± 7% and −21 ± 4%, respectively, $p = 0.63$).

Effects of SNP and ANP on contractile and diastolic properties

As shown in Fig. 2a, ANP significantly increased peak +d*P*/d*t* by 10 ± 3% ($p = 0.005$), whereas SNP had no influence ($p = 0.22$). The effects of ANP and SNP on diastolic properties are shown in Table 2. ANP and SNP tended to decrease Tau (−9 ± 3% and −7 ± 4%, respectively); however, these changes did not reach statistical significance ($p = 0.08$ and $p = 0.15$).

Table 2
Influence of SNP and ANP on hemodynamic variables.

	Control (before SNP)	SNP	Control 2 (before ANP)	ANP
LVSP (mmHg)	131.8 ± 9.5	111.6 ± 10.3*	138.0 ± 11.7	124.3 ± 8.5**
LVEDP (mmHg)	16.3 ± 2.5	13.0 ± 3.0	14.1 ± 1.3	11.0 ± 1.2
Peak +d*P*/d*t* (mmHg/s)	1904 ± 93	1832 ± 84	1842 ± 80	2018 ± 88**
CSF (ml/min)	88.4 ± 16.7	83.6 ± 15.8	86.4 ± 15.2	78.8 ± 15.2**
O_2 cont diff (vol%)	63.5 ± 2.0	62.1 ± 1.7	63.4 ± 1.9	62.0 ± 1.7
MVO_2 (J/min)	173.6 ± 25.9	162.8 ± 26.4	169.9 ± 23.5	157.9 ± 31.4
Peak −d*P*/d*t* (mmHg/s)	2209 ± 398	1443 ± 104*	1841 ± 158	1682 ± 110
Tau (ms)	48.1 ± 2.6	44.8 ± 3.4	46.4 ± 2.3	42.4 ± 2.5

SNP, sodium nitroprusside; ANP, atrial natriuretic peptide; LVSP, left ventricular systolic pressure; LVEDP, left ventricular end-diastolic pressure; Peak +d*P*/d*t*, peak positive d*P*/d*t*; CSF, coronary sinus blood flow; O_2 cont diff, coronary arteriovenous oxygen content difference; MVO_2, myocardial oxygen consumption; Peak −d*P*/d*t*, peak negative d*P*/d*t*; Tau, time constant of LV pressure decay during isovolumic relaxation.
Values are expressed as mean ± SEM.
* $p < 0.05$ vs control.
** $p < 0.05$ vs control 2.

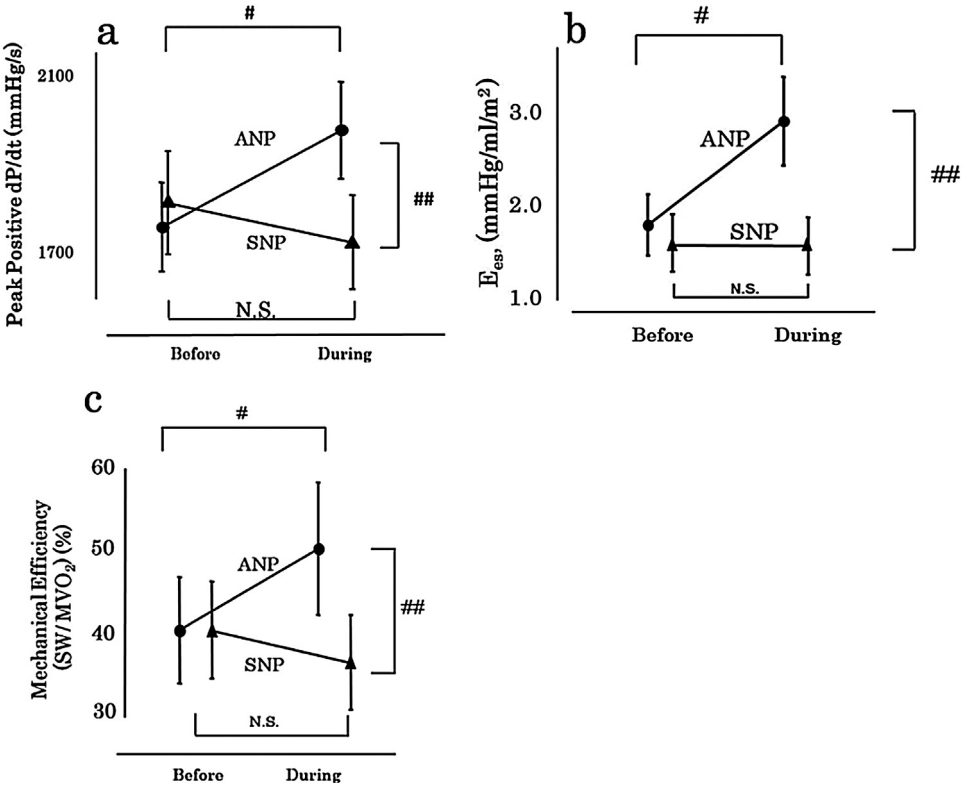

Fig. 2. Comparison of the response to the administration of SNP or ANP. (a) Comparison of the response to the administration of SNP or ANP on peak positive dP/dt using a paired t test ($^{\#}p < 0.05$). Two-way repeated measures ANOVA revealed a significant effect of ANP compared with SNP ($^{\#\#}p < 0.05$). (b) Comparison of the E_{es} response to the administration of SNP or ANP using a paired t test ($^{\#}p < 0.05$). Two-way repeated measures ANOVA revealed a significant effect of ANP compared with SNP ($^{\#\#}p < 0.05$). (c) Comparison of the SW/MVO$_2$ response to the administration of SNP or ANP using a paired t test ($^{\#}p < 0.05$). Two-way repeated measures ANOVA revealed a significant effect of ANP compared with SNP ($^{\#\#}p < 0.05$). Before, before administration of the drug; During, during administration of the drug; SNP, sodium nitroprusside; ANP, atrial natriuretic peptide; Peak +dP/dt, peak positive dP/dt; E_{es}, slope of the LV end-systolic pressure–volume relation; SW, stroke work (J) calculated as the area bound by the pressure–volume trajectory of 1 beat; MVO$_2$, myocardial oxygen consumption.

Effects of SNP and ANP on mechano-energetic variables

The LV ESPVR was obtained in 8 of 10 patients, because E_{es} was not measured in two subjects due to insufficient preload reduction during the Valsalva maneuver. Therefore, the influence of SNP and ANP on mechano-energetic variables was evaluated in eight subjects.

Representative pressure–volume loops before and after administration of SNP and ANP are shown in Fig. 3a and b. As shown in Table 3 and Fig. 2b, ANP increased E_{es} by 63 ± 24% (p = 0.0087) and decreased E_a by 11 ± 7%. These alterations resulted in potent improvement in ventriculoarterial coupling (from 1.47 ± 0.38 to 0.76 ± 0.14), although neither SNP nor ANP had a significant effect on the coronary arteriovenous oxygen content difference or MVO$_2$ (Table 3). ANP improved mechanical-energy transduction (SW/PVA) by 29 ± 5% (p = 0.0007) and mechanical efficiency (SW/MVO$_2$) by 25 ± 9% (p = 0.0073), as shown in Fig. 2c.

SNP had no significant effects on the mechano-energetic variables. SNP did not change E_{es}, E_a, leading to invariable ventriculo-arterial coupling. SNP did not change MVO$_2$, SW/PVA, or SW/MVO$_2$ (Table 3 and Fig. 2c). SNP slightly decreased SW (16 ± 6%), potential energy (35 ± 6%), and PVA (25 ± 5%).

Effects of SNP and ANP on plasma cGMP levels

The effects of SNP and ANP on plasma cGMP levels in the coronary sinus are shown in Fig. 4. Regardless of the infusion order of SNP and ANP, ANP administration significantly increased the plasma cGMP levels, whereas SNP had no effect.

Discussion

In the present study, we compared the effects of ANP with those of SNP on contractility and mechanical efficacy in patients with CHF associated with mild to moderate LV dysfunction using a conductance catheter. ANP infusion (0.05 μg/kg/min) and SNP infusion (0.3 μg/kg/min) similarly decreased LV systolic pressure and LVEDP; however, these two drugs had opposite effects on cardiac performance, including LV contractility, mechanical efficiency, and arterial–ventricular coupling. Intravenous infusion of ANP increased E_{es}, dP/dt, and SW, and decreased Tau and MVO$_2$ in patients with CHF. In contrast, SNP had no significant effects on these parameters. Thus, this is the first report demonstrating that ANP, but not SNP, improved systolic as well as diastolic properties in CHF patients. Furthermore, ANP significantly increased cardiac mechanical efficiency and ameliorated arterial–ventricular coupling in patients with LV dysfunction.

Several studies have investigated the effects of ANP on cardiac function. Lainchbury et al. reported that ANP exerts a positive inotropic effect in normal dogs where tissue cGMP levels would be expected to be low, and this positive inotropism disappeared in dogs with HF where tissue cGMP levels would be expected to be high [8]. On the other hand, Semigran et al. suggested that ANP has no direct effect on contractility function in the failed heart [18]. Given the fact that the expression levels of NPR-A are downregulated in CHF, the effects of ANP on LV contractility might be dependent upon the cardiac condition [8,19,20], and the positive inotropic effect of ANP might disappear when the severity of heart failure exceeds a certain threshold [9]. While the mean

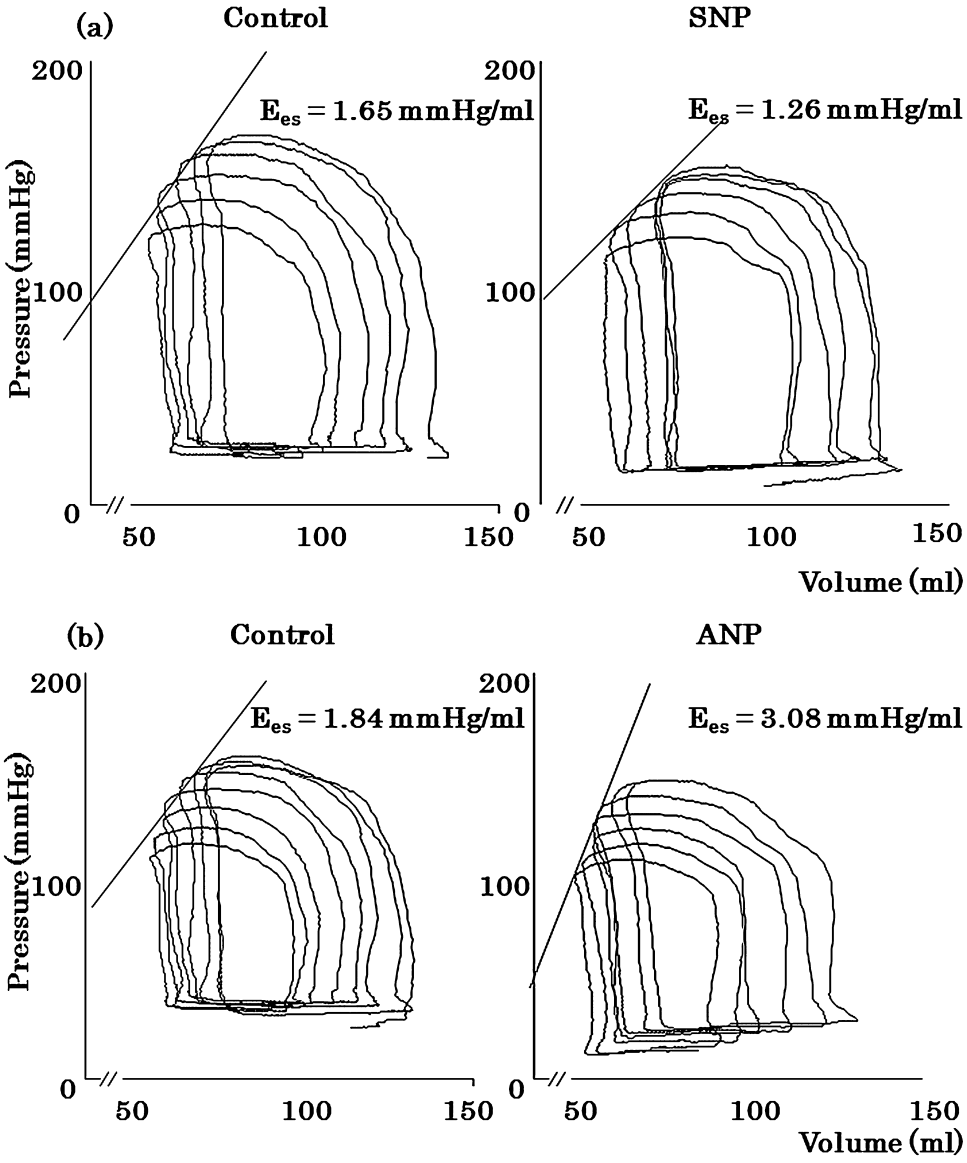

Fig. 3. Representative pressure–volume loops. (a) Representative pressure–volume loops following administration of SNP. (b) Representative pressure–volume loops following administration of ANP. SNP, sodium nitroprusside; ANP, atrial natriuretic peptide; E_{es}, slope of the LV end-systolic pressure–volume relation.

Table 3
Effect of SNP and ANP on mechano-energetic variables.

	Control (before SNP)	SNP	Control 2 (before ANP)	ANP
E_{es} (mmHg/ml/m^2)	1.26 ± 0.21	1.06 ± 0.15	1.30 ± 0.21	1.86 ± 0.32**
E_a (mmHg/ml/m^2)	1.29 ± 0.14	1.27 ± 0.20	1.55 ± 0.20	1.27 ± 0.16
Coupling	1.15 ± 0.13	1.23 ± 0.25	1.47 ± 0.38	0.76 ± 0.14**
SW (J/m^2/beat)	0.41 ± 0.05	0.35 ± 0.05	0.42 ± 0.05	0.45 ± 0.05
PVA (J/m^2/beat)	0.82 ± 0.11	0.61 ± 0.09*	0.66 ± 0.11	0.71 ± 0.10
SW/PVA (%)	51.5 ± 2.7	57.7 ± 2.9	51.6 ± 4.2	64.6 ± 3.0**
Peak +dP/dt (mmHg/s)	1904 ± 93	1832 ± 84	1842 ± 80	2018 ± 88**
MVO_2 (J/beat)	1.98 ± 0.28	1.86 ± 0.29	1.94 ± 0.26	1.80 ± 0.35
SW/MVO_2 (%)	40.5 ± 5.8	36.6 ± 5.7	40.5 ± 6.4	50.3 ± 8.0**
CSF (ml/min)	88.4 ± 16.7	83.6 ± 15.8	86.4 ± 15.2	78.8 ± 15.2**
O_2 cont diff (vol%)	63.5 ± 2.0	62.1 ± 1.7	63.4 ± 1.9	62.0 ± 1.7

SNP, sodium nitroprusside; ANP, atrial natriuretic peptide; E_{es}, slope of end-systolic pressure–volume relation; E_a, effective arterial elastance; Coupling, ventriculoarterial coupling; SW, stroke work; PVA, systolic pressure–volume area; Peak +dP/dt, peak positive dP/dt; MVO_2, myocardial oxygen consumption; CSF, coronary sinus blood flow; O_2 cont diff, coronary arteriovenous oxygen content difference.
Values are expressed as mean ± SEM.
* $p < 0.05$ vs control.
** $p < 0.05$ vs control 2.

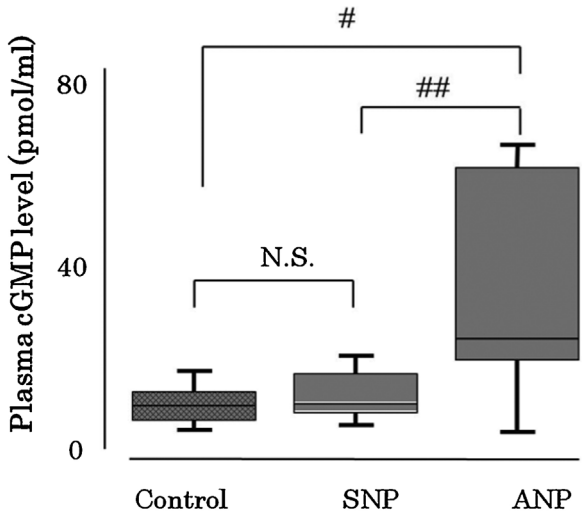

Fig. 4. The effects of SNP and ANP on plasma cGMP levels. $^{\#}p < 0.05$ compared with control, $^{\#\#}p < 0.05$ compared with SNP. SNP, sodium nitroprusside; ANP, atrial natriuretic peptide; cGMP, guanosine 3′,5′-cyclic monophosphate.

value of the EF in the present study was 0.45, it was 0.13 in the study by Semigran et al. [18]. Baseline differences in the patient population, especially in terms of residual LV function, might be one explanation for the discrepancy between our observation and theirs.

NO donors, like SNP, activate the soluble guanylyl cyclase system to generate cGMP. Although many experimental studies have attempted to clarify the influence of the NO/cGMP-dependent signaling pathway on cardiac function, there is much controversy. De Mulder et al. and Prendergast et al. reported that NO donors enhance systolic function in the β-adrenergic condition in rabbit hearts or in isolated guinea pig heart, respectively [1,21]. Paolocci et al. showed that HNO/NO– has positive inotropic actions in failing hearts of dogs [22]. In contrast, others have proposed that cGMP does not have a strong influence on cardiac contractility. Sandirasegarane and Diamond demonstrated that attenuation of cardiac contractility by NO donors in vivo occurs by a mechanism independent of cGMP [23]. Afzal et al. reported that cGMP exerts positive inotropism in failing rat cardiac ventricle [24]. Thus, questions remain regarding the actions of exogenous NO on cardiac function. These different findings might be due to some difference in the experimental conditions, such as the state of cardiac function, bioavailability of exogenous NO donors, etc.

Both ANP and SNP utilize cGMP as an intracellular second messenger, but the cardiac effects induced by these two agents are quite different. In the present study, ANP improved cardiac function and mechanical efficiency, whereas SNP had little effect on cardiac function, although the depressant effects induced by the two agents were similar. There are several possible explanations for the difference between ANP and SNP action, e.g. the compartmentalization of cGMP and indirect effects of ANP, such as anti-inflammatory and anti-oxidative activities. First, a difference in intracellular localization of cGMP produced by ANP and SNP should be examined. Castro et al. demonstrated that ANP and NO donors have different effects on cardiac and vascular smooth muscle function, and they speculated that these differences are due to the intracellular compartmentalization of cGMP and the role of phosphodiesterase (PDE) subtypes, that is, PDE5 controls the soluble pool and PDE2 exclusively controls the particulate pool [25,26]. Stasch et al. demonstrated that SNP increases cGMP in aortic tissue but not in noradrenaline-precontracted isolated rabbit aorta, on the other hand, ANP causes cGMP production in the aortic tissue as well as its surrounding bath solution [27]. These results suggest that cGMP produced via soluble guanylyl cyclase by SNP might not be extruded from the cell, but compartmentalized into some intracellular spaces. The difference in the intracellular localization of cGMP induced by SNP and ANP could lead to different cellular responses. Indeed, administration of ANP induces marked elevations in the plasma cGMP levels in the coronary sinus, whereas administration of SNP does not, although these two reagents had similar vasodilatory effects.

Second, Kiemer et al. demonstrated that ANP attenuated tissue necrosis factor-α production of lipopolysaccharide-activated macrophages via cGMP in mouse bone marrow macrophages, indicating that ANP has potent anti-inflammatory and anti-atherogenic properties [4]. It is possible that the positive inotropic effects of ANP observed in CHF are mediated by anti-inflammatory and anti-oxidative stress [28].

In the present investigation, we demonstrated that ANP significantly improved mechanical efficiency in the heart. Theoretically, when E_{es} equals E_a, the LV can yield to maximum SW [15,17,29]. Furthermore, Burkhoff and Sagawa showed that when E_a/E_{es} is approximately 0.5, the LV adapts to its afterload to make use of maximum mechanical efficiency [30]. In the present study, we demonstrated that ANP decreased E_a/E_{es} close to 0.5, whereas SNP did not (Table 3). Thus, ANP improved the mechano-energetics in patients with LV dysfunction. Therefore, therapeutic use of ANP is expected to exert positive inotropism, vasodilatory effects, and improvement in arterial–ventricular coupling in patients with LV dysfunction.

Furthermore, cGMP signaling exerts profound effects on the metabolism pathway in mitochondria of cardiomyocytes [31]. It is possible that the cGMP-dependent pathway activated by ANP might directly affect oxidative phosphorylation in the mitochondria. Thus, ANP may decrease MVO_2 independently of PVA.

Study limitations

Based on our preliminary study, the doses of SNP and hANP were set at 0.3 μg/kg/min and 0.05 μg/kg/min, respectively, because the systemic blood pressure depressant effects were equivalent at these doses. Ideally, the effects of various doses of SNP and hANP should be examined using a larger numbers of patients. In the present study, however, the investigation was performed in patients with heart failure; therefore, the numbers of participants and tolerable period for measurement were limited.

There are two methods to reduce the preload for the estimation of LV function by PV-loop, that is, (1) inferior vena cava (IVC) occlusion by a balloon catheter and (2) Valsalva maneuver. The IVC occlusion is a more effective method for reduction of preload compared with Valsalva maneuver. However, the mechanical reduction of IVC occlusion is not a physiological method. Furthermore, the IVC occlusion method is more invasive. Therefore, we chose Valsalva maneuver in order to alleviate the burden of the subjects. According to Mizuno's study [9], it is reported that E_{es} was 1.9 with IVC occlusion method. In the present investigation, E_{es} was normalized by body surface area, and before the correction, E_{es} was 2.1. From these points, our methodology and data are acceptable.

Conclusion

We demonstrated that ANP augmented cardiac contractility, improved arterial–ventricular coupling and cardiac mechanical efficiency, in patients with mild to moderate LV systolic dysfunction. These myocardial responses were not observed with SNP administration. Moreover, ANP improved diastolic function in these patients as well as SNP. The precise molecular mechanisms whereby ANP (or cGMP) augments contractility remain to be

determined; however, our finding confirmed that ANP is suitable for the treatment of patients with CHF.

Conflict of interest

None of the authors have a conflict of interest to disclose.

Funding source

We have no financial disclosure to declare in conjunction with the present work.

References

[1] De Mulder PA, De Hert SG, Van Kerckhoven RJ, Adriaensen HF, Gillebert TC. Sodium nitroprusside enhances in vivo left ventricular function in β-adrenergically stimulated rabbit hearts. Cardiovasc Res 1998;38:133–9.
[2] Shinke T, Takaoka H, Takeuchi M, Hata K, Kawai H, Okubo H, Kijima Y, Murata T, Yokoyama M. Nitric oxide spares myocardial oxygen consumption through attenuation of contractile response to beta-adrenergic stimulation in patients with idiopathic dilated cardiomyopathy. Circulation 2000;101:1925–30.
[3] Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998;339:321–8.
[4] Kiemer AK, Hartung T, Vollmar AM. cGMP-mediated inhibition of TNF-α production by the atrial natriuretic peptide in murine macrophages. J Immunol 2000;165:175–81.
[5] Wada A, Tsutamoto T, Matsuda Y, Kinoshita M. Cardiorenal and neurohumoral effects of endogenous atrial natriuretic peptide in dogs with severe congestive heart failure using a specific antagonist for guanylate cyclase-coupled receptors. Circulation 1994;89:2232–40.
[6] Calderone A, Thaik CM, Takahashi N, Chang DL, Colucci WS. Nitric oxide, atrial natriuretic peptide, and cyclic GMP inhibit the growth-promoting effects of norepinephrine in cardiac myocytes and fibroblasts. J Clin Invest 1998;101:812–8.
[7] Ohte N, Cheng CP, Suzuki M, Little WC. Effects of atrial natriuretic peptide on left ventricular performance in conscious dogs before and after pacing-induced heart failure. J Pharmacol Exp Ther 1999;291:589–95.
[8] Lainchbury JG, Burnett Jr JC, Meyer D, Redfield MM. Effects of natriuretic peptides on load and myocardial function in normal and heart failure dogs. Am J Physiol Heart Circ Physiol 2000;278:H33–40.
[9] Mizuno O, Onishi K, Dohi K, Motoyasu M, Okinaka T, Ito M, Isaka N, Nakano T. Effects of therapeutic doses of human atrial natriuretic peptide on load and myocardial performance in patients with congestive heart failure. Am J Cardiol 2001;88:863–6.
[10] Baim DS, Rothman MT, Harrison DC. Simultaneous measurement of coronary venous blood flow and oxygen saturation during transient alterations in myocardial oxygen supply and demand. Am J Cardiol 1982;49:743–52.
[11] Sohn IS, Lee JB, Park JH, Cho JM, Kim CJ. Valsalva maneuver to predict dynamic intraventricular obstruction during dobutamine stress echocardiography in patients with hypertension. Int J Cardiol 2010;144:433–5.
[12] Little WC, Barr WK, Crawford MH. Altered effect of the Valsalva maneuver on left ventricular volume in patients with cardiomyopathy. Circulation 1985;71:227–33.
[13] Takaoka H, Takeuchi M, Odake M, Hayashi Y, Hata K, Mori M, Yokoyama M. Comparison of hemodynamic determinants for myocardial oxygen consumption under different contractile states in human ventricle. Circulation 1993;87:59–69.
[14] Suga H, Sagawa K. Instantaneous pressure–volume relationships and their ratio in the excised, supported canine left ventricle. Circ Res 1974;35:117–26.
[15] Sunagawa K, Maughan WL, Sagawa K. Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. Circ Res 1985;56:586–95.
[16] Raff GL, Glantz SA. Volume loading shows left ventricular isovolumic relaxation rate: evidence of load-dependent relaxation in the intact dog heart. Circ Res 1981;48(6 Pt 1):813–24.
[17] Suga H. Ventricular energetics. Physiol Rev 1990;70:247–77.
[18] Semigran MJ, Aroney CN, Herrmann HC, Dec Jr GW, Boucher CA, Fifer MA. Effects of atrial natriuretic peptide on myocardial contractile and diastolic function in patients with heart failure. J Am Coll Cardiol 1992;20:98–106.
[19] Kojda G, Kottenberg K, Nix P, Schlüter KD, Piper HM, Noack E. Low increase in cGMP induced by organic nitrates and nitrovasodilators improves contractile response of rat ventricular myocytes. Circ Res 1996;78:91–101.
[20] Tsutamoto T, Kanamori T, Morigami N, Sugimoto Y, Yamaoka O, Kinoshita M. Possibility of downregulation of atrial natriuretic peptide receptor coupled to guanylate cyclase in peripheral vascular beds of patients with chronic severe heart failure. Circulation 1993;87:70–5.
[21] Prendergast BD, MacCarthy P, Wilson JF, Shah AM. Nitric oxide enhances the inotropic response to beta-adrenergic stimulation in the isolated guinea-pig heart. Basic Res Cardiol 1998;93:276–84.
[22] Paolocci N, Katori T, Champion HC, St John ME, Miranda KM, Fukuto JM, Wink DA, Kass DA. Positive inotropic and lusitropic effects of HNO/NO– in failing hearts: independence from beta-adrenergic signaling. Proc Natl Acad Sci U S A 2003;100:5537–42.
[23] Sandirasegarane L, Diamond J. The nitric oxide donors, SNAP and DEA/NO, exert a negative inotropic effect in rat cardiomyocytes which is independent of cyclic GMP elevation. J Mol Cell Cardiol 1999;31:799–808.
[24] Afzal F, Qvigstad E, Aronsen JM, Moltzau LR, Sjaastad I, Skomedal T, Osnes JB, Levy FO. Agents increasing cyclic GMP amplify 5-HT4-elicited positive inotropic response in failing rat cardiac ventricle. Naunyn Schmiedebergs Arch Pharmacol 2011;384:543–53.
[25] Castro LR, Verde I, Cooper DM, Fischmeister R. Cyclic guanosine monophosphate compartmentation in rat cardiac myocytes. Circulation 2006;113:2221–8.
[26] Takimoto E, Belardi D, Tocchetti CG, Vahebi S, Cormaci G, Ketner EA, Moens AL, Champion HC, Kass DA. Compartmentalization of cardiac beta-adrenergic inotropy modulation by phosphodiesterase type 5. Circulation 2007;115:2159–67.
[27] Stasch JP, Kazda S, Neuser D. Different effects of ANP and nitroprusside on cyclic GMP extrusion of isolated aorta. Eur J Pharmacol 1989;174:279–82.
[28] Ekelund UE, Harrison RW, Shokek O, Thakkar RN, Tunin RS, Senzaki H, Kass DA, Marbán E, Hare JM. Intravenous allopurinol decreases myocardial oxygen consumption and increases mechanical efficiency in dogs with pacing-induced heart failure. Circ Res 1999;85:437–45.
[29] Sunagawa K, Maughan WL, Burkhoff D, Sagawa K. Left ventricular interaction with arterial load studied in isolated canine ventricle. Am J Physiol 1983;245(5 Pt 1):H773–80.
[30] Burkhoff D, Sagawa K. Ventricular efficiency predicted by an analytical model. Am J Physiol 1986;250(6 Pt 2):R1021–27.
[31] Costa AD, Pierre SV, Cohen MV, Downey JM, Garlid KD. cGMP signalling in pre- and post-conditioning: the role of mitochondria. Cardiovasc Res 2008;77:344–52.